Successful Treatment of a Patient with Multicentric Castleman’s Disease who Presented with Thrombocytopenia, Ascites, Renal Failure and Myelofibrosis Using Tocilizumab, an Anti-Interleukin-6 Receptor Antibody

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Abstract

We herein describe an unusual case of multicentric Castleman’s disease accompanied by thrombocytopenia, ascites, renal failure and myelofibrosis in a Japanese woman. The patient was initially diagnosed as having myelodysplastic syndrome with myelofibrosis. The general condition of the patient deteriorated rapidly; however, treatment with tocilizumab, an anti-interleukin-6 receptor antibody, together with corticosteroids dramatically improved her symptoms. The clinical features of this case were similar to those of three cases previously reported by Takai et al. (Rinsho Ketsueki, 2010, 51:320-5), which were determined to be thrombocytopenia, anasarca, fever, reticulin myelofibrosis and organomegaly (TAFRO) syndrome, a possibly distinct clinical entity.

Key words: Castleman’s disease, systemic lupus erythematosus, interleukin-6, myelofibrosis, TAFRO syndrome

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Introduction

Castleman’s disease (CD), a rare polyclonal lymphoproliferative disorder originally described by Dr. Benjamin Castleman in 1956, is characterized by a typical histopathology of the involved lymph nodes (1). The originally described type was the hyaline-vascular type; later, a variant type rich in plasma cells was also described (2). Most cases of the hyaline-vascular type of CD involve a single or localized group of lymph nodes (unicentric CD) and can be asymptomatic. In contrast, plasma cell type CD frequently involves multiple lymphoid regions (multicentric CD, [MCD]) and is usually accompanied by various systemic inflammatory symptoms, such as fever, weight loss and night sweats. Interleukin-6 (IL6) is thought to play a central role in the clinical manifestations of MCD (3). In Western countries, HIV and human herpes virus-8 (HHV-8) infections play important roles in the pathogenesis of a large number of MCD cases, the prognosis of which is generally unfavorable (4-7). In contrast, tests for these viruses are seldom positive in Japan, and the disease progression is generally slow (8).

We encountered an unusual case of MCD accompanied by thrombocytopenia, massive ascites, renal failure and reticulin myelofibrosis. The patient was initially diagnosed as having myelodysplastic syndrome with myelofibrosis based on the histopathological findings of a bone marrow biopsy. The general condition of the patient deteriorated rapidly until a diagnosis of MCD was made. Later, the patient was successfully treated with corticosteroids and tocilizumab, an anti-IL6 receptor antibody.

Case Report

A 47-year-old Japanese woman was admitted to Kyoto University Hospital with a tentative diagnosis of myelodys-
AT THE FIRST VISIT: On admission: At 2.5 years after onset

<table>
<thead>
<tr>
<th>Test</th>
<th>At the first visit</th>
<th>On admission</th>
<th>At 2.5 years after onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (×10^9 per μL)</td>
<td>8.5</td>
<td>7.3</td>
<td>7.5</td>
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<tr>
<td>Red blood cells (×10^6 per μL)</td>
<td>5.03</td>
<td>3.53</td>
<td>4.91</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8</td>
<td>9.1</td>
<td>12.9</td>
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<td>Hematocrit (%)</td>
<td>41.5</td>
<td>27.5</td>
<td>41.7</td>
</tr>
<tr>
<td>Reticulocytes (×10^3 per μL)</td>
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<td>19</td>
<td>45</td>
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<tr>
<td>Platelet counts (×10^9 per μL)</td>
<td>98</td>
<td>39</td>
<td>286</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>12</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>15</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>229</td>
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<td>134</td>
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<tr>
<td>ALP (IU/L)</td>
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<tr>
<td>IgG (mg/dL)</td>
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<td>1,339</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>3.6</td>
<td>2.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.5</td>
<td>1.4</td>
<td>0.7</td>
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<td>CRP (mg/dL)</td>
<td>6.2</td>
<td>12.4</td>
<td>0.1</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>NA</td>
<td>21.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Abbreviations: AST: aspartate aminotransferase (reference range, 13–29 IU/L), ALT: alanine aminotransferase (reference range, 8–28 IU/L), LDH: lactate dehydrogenase (reference range, 129–241 IU/L), ALP: alkaline phosphatase (reference range, 115–359 IU/L), NA: not analyzed

The patient had been experiencing right subcostal pain, fever and general malaise for five weeks before admission. Three weeks before admission, she visited a local hospital where she underwent a series of medical tests. At the first visit, laboratory test results revealed mild thrombocytopenia and elevation of C-reactive protein (CRP) (Table). An abdominal computed tomography (CT) scan revealed hepatosplenomegaly with a small amount of ascites. After the initial examination, the patient was administered antibiotics and acetaminophen; however, her low-grade fever and general malaise persisted, and generalized edema gradually developed. Because the follow-up blood tests showed microcytic anemia and progressive thrombocytopenia, a bone marrow examination was performed. A dry tap was encountered on aspiration, and the bone marrow biopsy revealed an increased number of megakaryocytes, including micro- and multi-separated nuclear megakaryocytes, and reticulin fibrosis. On admission to Kyoto University Hospital, the patient’s body temperature was 37.6°C, severe pitting edema was present in both legs and the abdomen was markedly distended due to ascites. No skin lesions were observed. The patient was unable to walk due to the edema and leg weakness. Her superficial lymph nodes were not palpable. A CT scan revealed massive ascites, bilateral pleural effusions and systemic lymphadenopathy (Fig. 1A, B). Based on these findings, the patient was tentatively diagnosed as having myelodysplastic syndrome with myelofibrosis. She was referred to Kyoto University Hospital for allogeneic stem cell transplantation.

On admission to Kyoto University Hospital, the patient’s body temperature was 37.6°C, severe pitting edema was present in both legs and the abdomen was markedly distended due to ascites. No skin lesions were observed. The patient was unable to walk due to the edema and leg weakness. Her superficial lymph nodes were not palpable. A CT scan revealed massive ascites, bilateral pleural effusions and systemic lymphadenopathy (Fig. 1A, B). Blood tests revealed microcytic anemia, thrombocytopenia, renal dysfunction and an elevated serum CRP level (Table). The serum IgG level was 1,426 mg/dL, while that of IgG4 was 113 mg/dL, and no monoclonal bands were observed on immunofixation tests. The serum complement level was elevated. Tests for antinuclear, DNA, Sm, Jo1, ribonucleoprotein (RNP), C1q, hu-
man leukocyte antigen (HLA) and platelet antibodies were all negative, and the serum levels of IgG rheumatoid factor, proteinase 3-anti-neutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA were not elevated. The serum soluble interleukin-2 receptor (sIL2R) level increased to 1,592 U/mL. Repeated blood cultures were sterile. Both QuantiFERON-TB and β-D-glucan test results were negative. Chlamydia DNA obtained from a cervical specimen was not amplified by polymerase chain reaction (PCR). Anti-HIV, human T-lymphotropic virus (HTLV)-1 and hepatitis C virus antibodies and hepatitis B surface antigen test results were all negative. Moreover, PCR tests did not detect the presence of Epstein-Barr virus or HIV-8 in the patient’s blood. The serum IL6 level was elevated to 21.9 pg/mL. The bone marrow biopsy was repeated, and the specimen was ground for a flow-cytometric analysis, which did not detect any atypical phenotype populations.

After admission, a continuous fever ranging between 38°C and 39°C persisted, and frequent platelet and occasional red blood cell transfusions were required (Fig. 3). Additionally, the patient’s renal function rapidly deteriorated. Seven days after admission, an 18-fluoro-deoxyglucose (FDG) positron emission tomography (PET) scan was performed. Weak FDG uptake by the spleen and bilateral cervical, axillary and abdominal para-aortic lymph nodes was observed (Fig. 2C, D). On day 16, oliguria developed, and intravenous administration of furosemide and albumin was started. On day 17, hemodialysis was initiated because the patient’s urine volume had decreased to below 50 mL/day. After day 18, occasional drainage of the ascites and pleural effusion was administered to relieve the patient’s abdominal distension. The ascites and pleural fluid were exudative but sterile, and no lymphoma or other malignant cells were detected in the samples. From day 19 onwards, prednisolone was administered intravenously at 1 mg/kg. The continuous fever declined; however, the patient’s performance status remained very poor (grade 4 according to the World Health Organization classification). On day 22, a biopsy of the right cervical lymph node was performed. On the same day, methylprednisolone pulse therapy at a dose of 1,000 mg/day for three consecutive days was initiated. A histopathological examination of the lymph node revealed that the follicular structure was unclear and that plasma cells had proliferated in the presumed pericortical and medullary regions and infiltrated beyond the capsule (Fig. 1C, D). These findings were consistent with the manifestations of plasma cell type CD, although these were not typical. A flow cytometric analysis of the lymph node cells revealed a normal kappa/lambda light
The initial manifestation observed in the current case was fever, the etiology of which was not identified despite the use of various examinations. The common etiologies of fever of unknown origin include infectious diseases, such as tuberculosis, neoplastic diseases, such as malignant lymphoma and myeloid neoplasms, autoimmune diseases and drug fever. Initially, the patient was diagnosed with myelodysplastic syndrome based on the histopathological findings of bone marrow biopsies. Systemic lymphadenopathy was observed on a CT scan, and an elevated serum sIL2R level suggested a possible diagnosis of malignant lymphoma. Because the size of the lymph nodes was relatively small, approximately 1 cm in diameter, the lymph nodes exhibited only modest FDG uptake and the patient had severe thrombocytopenia, we did not perform a lymph node biopsy until the symptoms deteriorated. Based on the patient’s clinical course and the histopathological findings of the lymph node, however, neoplastic diseases were unlikely to have caused her symptoms. Systemic lupus erythematosus (SLE) was another possible diagnosis due to the existence of thrombocytopenia, exudative pleural effusion and renal dysfunction, although the patient’s symptoms and laboratory data did not fulfill the criteria for the classification of SLE (9). The patient’s condition deteriorated rapidly after admission; thus, we tentatively assumed that she had SLE and initiated corticosteroid therapy. Her initial response to this therapy was disappointing; severe thrombocytopenia persisted, the renal failure progressed and hemodialysis was started. Based on the histopathological findings of the lymph node biopsies, the laboratory data and other clinical manifestations, we diagnosed the patient as having MCD even though the presentation was not typical of the condition. After adding tocilizumab to the corticosteroid therapy, the patient’s symptoms, particularly the renal dysfunction and thrombocytopenia, dramatically improved (Fig. 3).

We speculate that the thrombocytopenia observed in this patient was caused by the destruction of platelets, since the patient’s response to platelet transfusion was very poor and the number of bone marrow megakaryocytes increased, consistent with the symptoms of autoimmune thrombocytopenic purpura (ITP). Kojima et al. reported similar MCD cases with ITP and pleural effusions (10). MCD is likely a morphologic syndrome uniting a group of diseases with various etiologies and is reported to be occasionally associated with autoimmune manifestations and connective tissue diseases (11).

Another case of MCD accompanied by ascites, pleural effusion and thrombocytopenia was recently reported by Awano et al. (12). As observed in our case, the serum IL6 level was only slightly elevated despite a marked increase in the serum level of CRP. The clinical course of the patient was also similar to that of our patient. The patient was initially treated with corticosteroid therapy, including methylprednisolone pulse therapy; however, the platelet count decreased and ascites progressively increased. The administr-
Conducting a nationwide survey would be useful for clarifying the clinical and pathological features of this syndrome.

The authors state that they have no Conflict of Interest (COI).

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References